INT. J. QUANTUM CHEM.: QUANTUM BIOLOGY SYMP NO. 3, 45-50 (1976)

The Electronic Theory of Cancer

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Introduction

Cancer research was retarded by our looking at cancer as a disease which has to be cured, instead of looking at it as a fascinating natural phenomenon which has to be understood. To understand it, we have to take it out of the narrow confines of medicine and place it into the wide framework of natural philosophy.

The history of life is sharply divided in two parts, separated by the appearance of light and oxygen. We will call the first anaerobic spell the α, the second aerobic epoch the β period.

Life originated on a dark and airless globe covered by dense water vapor. There was no light and no oxygen. We know very little about life in this first dark and airless α period. We can only philosophize that under its very inhospitable conditions life could have developed, but as the simplest systems which could perform only the simplest "vegetative" functions, like proliferation and fermentation, which demand no structures. To make life perennial, the living systems had to proliferate as fast as conditions permitted, producing energy by fermentation.

When light appeared, life began to develop and differentiate, to build increasingly complex structures which could perform increasingly complex functions. The problem is, how could light induce this change? What the living systems did with light was to use its energy to decompose water into its elements, hydrogen and oxygen, linking the H to carbon, creating foodstuffs, while releasing the O as O_2 into the atmosphere. It could recover the invested energy by oxidizing the H with the O_2 to water again. What was left behind was only H, O, and energy. O. Warburg thought that it was the energy which transformed the living systems. We find it difficult to accept this opinion as a full explanation, because energy can drive, but not build mechanisms. So we are left with O as the only factor which could transform the living systems by transforming their proteins, and the question is, how could O_2 do it?

There being no oxygen in the α period, the atmosphere had to be strongly reducing, dominated by electron donors, substances which could donate electrons. At the resulting high electron pressure the orbitals and energy levels of the protein molecules had to be fully occupied, leaving no room for motion, conduction, all this making the protein consist of well-balanced "closed-shell" dielectric molecules which had no uncompensated forces that could link these molecules together to complex structures. The living systems had to consist thus of dissolved molecules in molecular dispersion, which could perform simple chemical reactions such as breaking and making bonds, by which a relatively small part of the energy of the foodstuff molecules could be released. This simple method of energy

production, which can be performed by dissolved molecules in molecular dispersion, is fermentation.

Oxygen is an oxidizing agent, an electron acceptor which opens the possibility that it could transform the protein by taking electrons out of it, desaturating the energy band, and uncoupling electron pairs, thus transforming the protein molecules into conductors and highly reactive free radicals, creating unbalanced forces by which the single molecules could be joined to complex integrated structures which could transduce chemical energy into work, be this work mechanical (motion), osmotic (membrane activity), or electric (nervous action). The structures could also build water structures around themselves.

When Nature develops a new system, she does not throw the old one out but builds the new one on top. So she did not throw out the system of dissolved closed-shell dielectric molecules developed in the α period, but used their system as a matrix into which she placed the structures developed in the β period, letting the dissolved molecules of the α period perform their simple function and cater for the structures, which produced energy by releasing, oxidatively, the energy of the products of fermentation.

In order to preserve the harmony of the whole of the increasingly complex living systems, the unbridled proliferation had to be suppressed and replaced by regulation that allowed the cells to divide only if there was need for it. Cell division must have been interferred with in the β period by structures, but, in addition, a regulatory system had to be developed which suppressed cell division completely until there was need for it. It could be suppressed by binding the highly reducing SH groups involved in protein synthesis.

To start up a cell division, the SH had to be liberated and the structures had to be dismantled. Oxidation being linked to structure, the cell had to turn for energy to fermentation which demands no structure. All this could be summed up by saying that, in order to divide, the cell had to turn back, to a great extent, to the proliferative-fermentative α state.

After the division is completed the β state has to be built up again. If the road of return is perturbed, or if, by any factor, the β state is made unstable, then the cell has to persist in the proliferative α state and tumor has to result.

The objection was raised that this whole outlook has to be wrong, because highly reactive and mobile electrons of conducting protein radicals should easily interact with photons, which would make the protein colored, while the great number of isolated and thoroughly studied proteins was found to be colorless and transparent. This was a serious objection which, for us, made a puzzle out of the problem, and puzzles have their solutions. They only have to be found. The solution of this one is simple and amusing. It is this: The protein chemist needs crystals, and to produce them he needs protein solutions. So what he did was to extract from living systems the soluble proteins; he called the extracted material "the residue" and sent it down the drain, sending down the insoluble structures that performed the more complex biological functions which involve conduction and free radicals. He retained the closed-shell soluble molecules of the α period. So when embarking with J. McLaughlin on this line, we followed the opposite course, sent down the drain the soluble molecules and retained the structures, dissolving them by detergents. The solutions of the structural proteins of the rat liver had the color of a good Swiss chocolate.

Oxygen and Dicarbonyls

There were two major difficulties in supposing that it was oxygen which induced the α–β transformation by taking electrons out of the protein. One of these difficulties is that

O_2 or O are bivalent electron acceptors which tend to take electrons over pairwise, which leads to burning, oxidation, and not to the production of free radicals. The production of radicals demands monovalent acceptors which can uncouple electron pairs. The other difficulty was that the cell contains a great mass of proteins which demands a great mass of electron acceptors to be desaturated, while it can contain only a very small amount of monovalent acceptors, which could act as acceptors for protein only if they could transmit their accepted electrons to O_2.

Oxygen, O=O, can be made into a monovalent electron acceptor by linking its single O atoms to carbon C instead of linking them to one another. The resulting carbonyl, C=O, being small, cannot easily accommodate a whole electron, which makes it into a "weak" electron acceptor. It can be made into a "strong" electron acceptor by linking two C=O's together to a dicarbonyl in which the π electronic systems of the two conjugated double bonds fuse into a wider π system, which can easily accept a whole electron in the ground state and is thus a "strong" but still a monovalent acceptor. This makes our whole problem boil down to the question whether the cell can build up a free radical chain which can transmit, over dicarbonyls, electrons from protein to O_2 and activate O_2 to act as electron acceptor.

The transfer of an electron pair from one molecule to the other is "oxidation," burning. The transfer of a single electron is "charge transfer" which was looked upon till now as a rare item of Nature's curiosity shop, while the possibility of the existence of free radicals in living systems was denied altogether.

The simplest dicarbonyl is glyoxal [Fig. 1(a)], and the simplest derivative of glyoxal is methylglyoxal [Fig. 1(b)]. What makes this fact most exciting, is a discovery made more than sixty years ago by two English and a German scientists (H. D. Dakin, H. W. Dudley, and C. Neuberg) who discovered a most active and widely spread enzymic system, the "glyoxalase," which could transform methylglyoxal into the corresponding inactive D-lactic acid. Nature does not indulge in luxuries, and if there is such an enzymic system, it must have something important to do, but nobody knew what. Methylglyoxal is not only a good electron acceptor but it can also arrest cell division by forming hemimercaptals with SH groups involved in protein synthesis, as shown by L. Egyud and ourselves.

All this led us to mix protein with methylglyoxal in the presence of O_2, expecting vividly colored free radicals to be formed, but nothing happened. Either we followed a wrong trail, or else the situation was complex and demanded a thorough study. Should dicarbonyls react with protein, they would have to do so by interacting with amino nitrogen, and so we started our study with the interaction of dicarbonyls and simpler amines.

Interaction of Methylamine and Methylglyoxal

The simplest organic amine is methylamine, CH_3NH_2. If an aqueous solution of methylamine and methylglyoxal are mixed, a yellow Schiff base is formed:

$$RNH_2 + O{=}CR \leftrightarrow RN{=}CR + H_2O$$

which shows a strong absorption at the short end of the visible spectrum (Fig. 1, curve 3). No vivid colors are developed to indicate the formation of charge transfer and free radicals. However, the yellow color has a red tint. In the spectrum this complex is indicated by a hump at 475 nm (Fig. 2, curve 1). The red complex is not stable and the red tint and hump disappear on storage, the complex having gone over into the stable Schiff base. The experiment showed that the red coloration and the absorption at 475 nm depended on the dielectric properties of the solvent, on the degrees of freedom of the water dipoles.

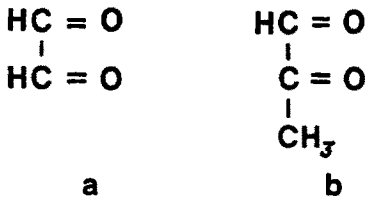

Figure 1.

In solvents of lower dielectric constant, like alcohol, acetone, dimethylsulfoxide, or glycerol, the mixture of amine and dicarbonyl assumed a deep red color which was fairly stable (Fig. 2, curve 2). The red complex could be obtained as a solid by mixing an acetone solution of methylamine and methylglyoxal. Both these reagents are soluble in acetone, but their complex is not, and so it precipitates and can be separated on the centrifuge. It gave a strong electron spin resonance signal which, on first approach, indicated two spins per complex. What happened was that the amine and dicarbonyls formed an un-

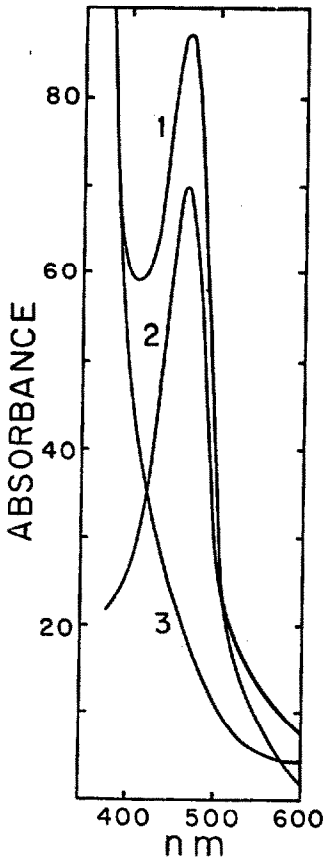

Figure 2.

stable charge transfer complex which, in the presence of water, went into a Schiff base, while in the absence of water it formed a charge transfer complex.

This complex is now under study. The experiments indicate that it can form very stable and highly colored complexes with protein, which suggests that electrons of the protein can be transferred through the amine-dicarbonyl onto O_2, leading to the formation of protein radicals.

Similar reactions could be demonstrated with biological amines, such as dopamine, serotonine, or noradrenaline. The radical complexes of these can also transfer electrons in photosynthesis. The experiments with biogenic amines also showed that peroxidase can catalyze the electron transfer. This means that peroxides are involved and the oxygen is fixed as a monosubstituted peroxide. Activation by the peroxidase means that the enzyme enables the O_2 to take up a second electron, being detached, eventually as hydrogen peroxide which, in tissues, can be expected to be decomposed by the catalase. This is interesting for two reasons. The one is that more than thirty years ago D. Keilin and E. F. Hartree discovered that catalase can not only decompose hydrogen peroxide, but it also can act as peroxidase. This becomes now intelligible. The other reason is that the inhibition of the catalase has to arrest electron transfer, and J. P. Greenstein discovered that cancer cells produce a factor which inhibits catalase. The inactivation of catalase must break the electron transfer and act as anoxia, which is carcinogenic (H. Goldblatt and G. Cameron).

To sum up, we can say that amines and dicarbonyls unite to an unstable charge transfer complex which can activate oxygen, and transfer electrons onto it. The trimeric amine-dicarbonyl-oxygen complex can complex with protein and transfer its electrons to oxygen, transforming it into a radical and conductor.

These experiments led to an observation which may have a major medical importance. They showed that the formation of the oxygen complex is autocatalytic, that is, the rate of its formation depends on its quantity already present. They also shed an unexpected new light on the role of O_2, which hitherto was thought to be connected with biological phenomena, but indirectly, through the production of energy. The presented experiments indicate that O_2 is part and parcel of the living machinery dominating its electronic structure. The experiments also establish a new basic parameter of life, the D/A quotient, the relation of donors and acceptors, with the resulting electron tension dominated by SH and dicarbonyls.

On Cancer

After this lengthy introduction we can ask: has all this anything to do with cancer? There is one simple approach to this question. As we have shown at the beginning, the electron transport and electronic desaturation of protein declares itself by the color due to electronic reactivity. So we can start simply by comparing the color of cancer with the color of the homologous normal tissue; we can compare, for instance, the color of the structure proteins of normal liver tissue of the rat with the color of the homologous preparation of the parenchymal liver tumor of the same animal. Our slide shows the structure proteins of the Morris Hepatoma 3924A and the analogous proteins of the normal liver of the same animal. As can be seen, the normal proteins are chocolate brown, while the tumor proteins are practically colorless, faintly yellow, indicating that the cancer was unable to build up or maintain its electron transfer chain. According to what we have said before, cancer must be produced by any factor which makes the cell unable to build up its electron transfer system. In this light cancer seems to be a cell in which the connection of structure and O_2 is broken. This conclusion is supported by the fact that cancer

cells show a low electron-spin resonance signal (B. Commoner, J. Townsend, and E. C. Page). This quality it shares with any dividing cell, which has to be in the α state. We have shown earlier that the cells of the regenerating rat liver are also relatively colorless, and so are embryonic tissues.

An endless number of factors can disturb the electron transfer chains and lead the cell into the cancerous α state. Disorder may do so by interferring with the buildup of water structures which stabilize charge transfer complexes. Disorder is very unspecific and can be produced by an endless number of factors, including asbestos and viruses. Cancer has to be produced by an overproduction of the Greenstein factor which cuts the electron transfer chain at its oxygen end. It can be produced by an overactive glyoxalase, which destroys the dicarbonyls, etc. A change in any of the discussed factors can lead into a vicious circle which the cell is unable to break without outside help.

Whether this new knowledge will lead to a cure of cancer cannot be predicted. What can be said with finality at present was stated by Bernal years ago: we can control only what we understand. The observations presented, contributing to our knowledge, may improve our chance to get rid of this scourge.

Acknowledgment

This work was supported by the National Foundation for Cancer Research,

Received January 16, 1976